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Impact of Polyvascular Disease on Clinical Outcomes in Patients Undergoing Coronary Revascularization: an observation from the CREDO-Kyoto Registry Cohort-2

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Abstract

Objective: Patients with coronary artery disease (CAD) often have prior stroke or concomitant extracardiac vascular disease (EVD) such as cerebral, aortic, or peripheral vascular disease. However, clinical outcomes after coronary revascularization in patients with polyvascular disease have not been fully elucidated.

Methods: Among 15263 patients undergoing first coronary revascularization enrolled in the CREDO-Kyoto registry Cohort-2 from January 2005 to December 2007, there were 1443 patients with prior stroke (stroke+CAD group), 974 patients with EVD (EVD+CAD group), 253 patients with both prior stroke and EVD (stroke/EVD/CAD group) and 12593 patients with neither prior stroke nor EVD (CAD alone group [reference]).

Results: The cumulative incidence of major adverse cardiovascular events (MACE: composite of cardiovascular death, myocardial infarction and stroke) through 3 years was significantly higher in patients with polyvascular disease compared with reference patients (19.9% in the stroke+CAD group, 18.5% in the EVD+CAD group, 20.1% in the stroke/EVD/CAD group, and 11.2% in the CAD alone group, P<0.0001). After adjusting confounders, the presence of EVD and/or stroke was independently associated with higher risk for MACE compared with the reference group (adjusted HR [95%CI]: 1.34 [1.17-1.54], P<0.0001 in the stroke+CAD group, 1.56 [1.32-1.84], P<0.0001 in the EVD+CAD group, and 1.66 [1.24-2.23], P=0.0007 in the stroke/EVD/CAD group). However, the presence of EVD and/or stroke was not associated with higher risk for myocardial infarction.

Conclusions: Clinical outcome after coronary revascularization was worse in patients with prior stroke and/or EVD, which was mainly driven by the increased risk for non-coronary cardiovascular events.

Key words: peripheral vascular disease, stroke, coronary artery disease, coronary stent, coronary artery bypass grafting

1. Introduction

Patients with coronary artery disease (CAD) often have prior stroke or concomitant cerebral, aortic or peripheral vascular disease. The presence of cerebrovascular disease is associated with higher prevalence of CAD [1-2]. The prevalence of CAD is also reported to be high in patients with aortic aneurysm [3-4]. It is also reported that asymptomatic CAD was found in 25% of the patients undergoing carotid endarterectomy [5]. Furthermore, peripheral artery disease (PAD) could be a marker for atherosclerotic involvement of the coronary arteries [1,6].

The Reduction of Atherothrombosis for Continued Health (REACH) registry is one of the largest international epidemiologic database for atherothrombotic disease [7]. This registry showed that patients with prior history of ischemic events at baseline had the highest rate of subsequent ischemic events [8]. Furthermore, patients with polyvascular disease were associated with higher risk for cardiovascular events. However, clinical outcomes after coronary revascularization in patients with polyvascular disease have not been fully elucidated, especially in patients with stable CAD [9-11]. In the current study, we analyzed the impact of prior stroke or extra-cardiac vascular disease (EVD) on cardiovascular outcomes in a large Japanese observational database of patients who underwent first coronary revascularization.

2. Methods

2.1. Study population

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) registry cohort-2 is a multi-center registry enrolling consecutive patients undergoing first coronary revascularization procedures among 26 centers in Japan between January 2005 and December 2007 (Supplemental Appendix A). The relevant review boards or ethics committees in all participating centers approved the research protocol. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

The design and patient enrollment of the CREDO-Kyoto PCI/CABG registry cohort-2 has been described previously [12]. A total of 15939 patients underwent PCI or CABG as the first coronary revascularization procedure during the 3 years of enrollment period. Excluding 67 patients who refused study participation, and 609 patients who underwent combined non-coronary surgery, 15263 patients (PCI: 13087, and isolated CABG: 2176) constituted the study population for the current analyses. Patients were divided into 4 groups according to the presence of prior stroke or EVD: 1443 patients with prior stroke (stroke+CAD group), 974 patients with EVD (EVD+CAD group), 253 patients with both prior stroke and EVD (stroke/EVD/CAD group) and 12593 patients with neither prior stroke nor EVD (CAD alone group [reference]). Among 1227 patients with EVD, 427 patients, 187 patients, and 702 patients had aortic disease, carotid artery disease and other peripheral vascular disease, either alone or in combination, respectively.

2.2. Definitions

Definitions of baseline clinical characteristics were described previously [12]. Prior stroke included both ischemic and hemorrhagic stroke and was defined as stroke with neurological symptoms lasting >24 hours. Therefore, transient ischemic attack was excluded from the prior stroke. EVD was regarded to be present when aortic, carotid, or other peripheral vascular disease such as iliac, femoral, popliteal, tibioperoneal, or renal artery disease were being treated or scheduled for surgical or endovascular interventions. Patients with medical treatment only were excluded. The primary outcome measure in the current analysis was major adverse cardiovascular events (MACE; a composite of cardiovascular death, myocardial infarction (MI), or stroke).

2.3. Data collection and follow-up

Demographic, angiographic, and procedural data were collected from hospital charts or databases according to pre-specified definitions by experienced clinical research coordinators in the independent research organization (Research Institute for Production Development, Kyoto, Japan) (Supplemental Appendix B). Follow-up data were obtained from hospital charts or by contacting patients, or referring physicians. Death, MI and stroke were adjudicated against original source documents by a clinical event committee (Supplemental Appendix C). Median follow-up duration was 946 (inter-quartile range: 675-1239) days. Two-year follow up was completed in 11891 patients (78%).

2.4. Statistical analysis

Variables were compared with analysis of variance. Continuous variables were expressed as mean value ± standard deviation. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test.

The adjusted risk for clinical outcomes was estimated by the Cox proportional hazard model by incorporating the presence of prior stroke, EVD and both of them together with the 32 clinically relevant factors shown in Table 1 as the risk adjusting variables to be consistent with our previous reports [12-13]. The continuous variables were dichotomized by clinically meaningful reference values or median values. Twenty-six centers were included in the model as stratification variables. In the Cox proportional hazard model, we developed dummy codes for presence of prior stroke, EVD and both of them with absence of prior stroke and EVD as the reference. The effect of each category compared to the reference category was expressed as hazard ratios (HR) and their 95% confidence intervals (CI).

Statistical analyses were conducted by two physicians (Morikami Y and Natsuaki M) and by a statistician (Morimoto T) with the use of JMP 8.0 (SAS Institute Inc, Cary, NC) and SAS 9.2 (SAS Institute Inc, Cary, NC) softwares. All the statistical analyses were two-tailed. P values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Because of the large sample size of the study, significant differences were observed in many baseline variables among the 4 groups. As compared with those patients with CAD alone, patients with EVD and/or stroke were the older and had lower body mass index. It is of note that prevalence of atrial fibrillation was higher in patients with prior stroke. Male gender, hypertension, diabetes, multivessel disease, unprotected left main coronary artery disease, target of chronic total occlusion, revascularization by CABG, chronic kidney disease, dialysis, anemia and malignancy were more prevalent in patients with EVD and/or stroke. In contrast, acute MI was more prevalent in patients with CAD alone. Statins, beta-blockers and thienopyridine were less frequently prescribed in patients with EVD and/or stroke, while calcium channel blockers, warfarin and proton pump inhibitors were more often used in patients with EVD and/or stroke (Table 1).

3.2. Clinical outcomes

Through 3-year follow-up, the cumulative incidence of MACE was significantly higher in patients with EVD and/or stroke as compared with patients with CAD alone (Table 2 and Figure 1). The cumulative incidences of all-cause death, cardiovascular death, non-cardiovascular death and stroke (both ischemic and hemorrhagic stroke) were also significantly higher in patients with EVD and/or stroke as compared with patients with CAD alone (Table 2 and Figure 1). Regarding oral

anticoagulant therapy, the cumulative incidence of hemorrhagic stroke tended to be higher in those patients receiving oral anticoagulant therapy at time of hospital discharge as compared with those not receiving it. The cumulative incidence of hemorrhagic stroke was significantly higher in patients with prior stroke and/or EVD than in patients with CAD alone regardless of the use of oral anticoagulant therapy (Supplemental Table). Regarding oral antiplatelet therapy, the cumulative incidence of hemorrhagic stroke was significantly higher in those with prior stroke and/or EVD than in those with CAD alone in patients receiving dual antiplatelet therapy at discharge (Supplemental Table). On the other hand, the cumulative incidence of MI was not significantly different across the 4 groups (Table 2). After adjusting confounders by multivariable analysis, the adjusted risks for MACE, all-cause death, non-cardiovascular death and stroke remained significantly higher in patients with EVD and/or stroke as compared with patients with CAD alone (Figure 2). In contrast, the adjusted risk of the 3 groups with EVD and/or stroke relative to the CAD alone group was neutral for MI and any coronary revascularization (Figure 2).

Regarding the causes of death during follow-up, cardiac death was the most frequent cause of death in each group. Vascular death was more often found in patients with EVD and/or stroke as compared with patients with CAD alone. There was no significant difference in the proportion of patients with non-cardiovascular death across the 4 groups (Table 3).

4. Discussion

The main findings of the current study are as follows: (1) Clinical outcome after coronary revascularization was worse in patients with prior stroke and/or EVD, which was mainly driven by the increased risk for non-coronary cardiovascular events; (2) However, the presence of EVD and/or stroke was not associated with higher risk for myocardial infarction.

In the current study, patients with EVD were found in 1227 patients (8%) including 253 patients with concomitant prior stroke. Presence of EVD has been reported to be an independent risk factor of long-term mortality in patients with CAD [14-16]. In consistent with these reports, coexistence of EVD with CAD was associated with higher risk for MACE, all-cause death, cardiovascular death, non-cardiovascular death and stroke after coronary revascularization in the current study.

In this study, 1696 patients (11%) had prior stroke including 253 patients with concomitant EVD. The presence of prior stroke was associated with higher risk for MACE, all-cause death, non-cardiovascular death and stroke after coronary revascularization. In consistent with our report, Mukherjee et al reported that patients with prior stroke had worse cardiovascular outcomes after acute coronary syndrome [10]. It is interesting to note that prevalence of atrial fibrillation was higher in patients with prior stroke in the current study. Significant proportion of prior and/or recurrent stroke might be embolic stroke related to atrial fibrillation. Systemic atherosclerotic burden in the stroke population might be less extensive as compared with that in the EVD population, leading to relatively lower excess risk of the stroke population compared to the EVD population.

Cumulative incidences of MACE, all-cause death, cardiovascular death, non-cardiovascular death and stroke were significantly higher in the stroke/EVD/CAD group compared with the CAD alone group, while those were generally similar across the 3 groups of patients with EVD and/or stroke. However, multivariate analysis showed that the risks for those outcomes were highest in patients with both prior stroke and EVD. These findings are consistent with previous reports. Mukherjee et al reported that the risk for death/MI/stroke was the highest in patients with PAD and prior stroke compared with those with either PAD or stroke [10]. Subherwal et al reported the impact of PAD and cerebrovascular disease (CVD) on long-term cardiovascular outcomes in patients with non-ST-segment elevation MI [17]. AS compared with the CAD alone group, patients with involvement of all 3 arterial beds had the highest risk for long-term mortality. These findings suggest that cardiovascular risk seems to be related to the number of arterial territories with significant atherosclerosis.

In the REACH registry, patients with polyvascular disease had significantly higher risk for cardiovascular events compared with those with risk factors only [8]. Furthermore, prior stoke was associated with higher risk for death, MI, or stroke, including both ischemic and hemorrhagic stroke in patients with coronary artery disease [18]. Despite greater prevalence of multivessel coronary artery disease, patients with prior stroke and/or EVD did not have excess risk for MI as compared with patients with CAD alone, while the risk for stroke was significantly higher in patients with prior stroke and/or EVD than in patients with CAD alone in this study. Cumulative incidences of both

cerebral infarction and cerebral hemorrhage were also significantly higher in patients with prior stroke and/or EVD than in patients with CAD alone. Therefore, the worse cardiovascular outcome in patients with prior stroke and/or EVD was mainly driven by the increased risk for non-coronary cardiovascular events. Lower incidence of MI relative to stroke in Japanese population might be one of the reasons for these results [19-20]. More liberal use of CABG as the mode of coronary revascularization might contribute to the prevention of MI in patients with prior stroke and/or EVD.

Despite higher risk for cardiovascular events, higher mortality in particular, in patients with polyvascular disease, several studies have highlited that relatively little attention had been paid in the detection of PAD [21-22]. Ankle-brachial index measurement identifies a large number of patients with previously unrecognized PAD. Ultrasonography is also a noninvasive examination and considered to be an effective method to detect the abdominal, carotid or renal artery disease. Given the markedly higher risk for cardiovascular events in patients with polyvascular disease, screening of EVD should be mandatory in patients with CAD. Furthermore, patients with polyvascular disease were less frequently treated with optimal medical therapies [11,21-23]. In consistent with these reports, statins were less frequently used in patients with polyvascular disease than in patients with CAD alone in this study. Further efforts should be directed towards better identification of EVD and optimal treatment to reduce the excess risks of CAD patients with concomitant stroke and/or EVD.

There are several limitations in this study. First, baseline characteristics were markedly different between patients with prior stroke and/or EVD, and patients with CAD alone. Second,

screening tests for EVD was left to the discretion of each attending physician. Therefore, the proportion of patients with polyvascular disease might be underestimated. Third, EVD included those involving various vascular territories. Clinical outcomes after coronary revascularization in patients with polyvascular disease might be different according to the vascular territories involved. Forth, patients with vascular diseases treated by medication only were excluded from EVD group in this study. However, it would be appropriate to evaluate clinically relevant polyvascular disease by the definitions of EVD being treated or scheduled for surgical or endovascular interventions. Fifth, there was no information about the timing of prior stroke. Finally, causes of cerebral infarction were not assessed in this study, and we could not distinguish cardioembolic, atherothrombotic, or lacunar infarction for both prior stroke and recurrent stroke.

In conclusion, clinical outcome after coronary revascularization was worse in patients with prior stroke and/or EVD, which was mainly driven by the increased risk for non-coronary cardiovascular events.

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Conflict of interest disclosure statement

There are no conflicts of interest to disclose.

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Figure legends

Fig. 1.

Cumulative incidence of (A) composite of CV death, MI and stoke and (B) all-cause death.

CV, cardiovascular; MI, myocardial infarction; CAD, coronary artery disease; EVD, extra-cardiac vascular disease.

Fig. 2.

Adjusted risk for clinical outcomes in the stroke+CAD, EVD+CAD, and stroke/EVD/CAD groups as compared with the CAD alone group.

CV, cardiovascular; MI, myocardial infarction; CAD, coronary artery disease; EVD, extra-cardiac vascular disease; HR, hazard ratio; CI, confidence interval.

Tables

Table 1

Baseline characteristics

	CAD Alone (N=12593)	Stroke and CAD (N=1443)	EVD and CAD (N=974)	Stroke/EVD/CAD (N=253)	P value
(A) Clinical characteristics					
Age (years)	67.5±11.0	71.9±9.4	71.3±9.2	72.3±7.7	<0.0001
Age ≥ 75 years*	29%	42%	42%	43%	<0.0001
Male*	71%	73%	80%	88%	<0.0001
BMI	23.8±3.4	23.3±3.5	22.7±3.4	22.6±3.0	<0.0001
BMI < 25.0*	68%	72%	78%	84%	<0.0001
Acute myocardial infarction*	34%	30%	12%	12%	<0.0001
Hypertension*	81%	87%	84%	89%	<0.0001
Systolic blood pressure	136±25.0	136±26.4	137±23.9	136±23.8	0.63
Diabetes mellitus*	38%	45%	41%	47%	<0.0001
Insulin therapy	8.2%	12%	12%	13%	<0.0001
Current smoking*	32%	22%	35%	19%	<0.0001
Heart failure*	20%	28%	17%	23%	<0.0001
Shock at presentation	5.4%	7.6%	3.9%	3.2%	0.0003
Mitral regurgitation grade 3/4*	3.7%	5.2%	4.5%	4.0%	0.04
Ejection fraction	58.5±13.3	56.2±14.0	59.5±13.7	59.4±13.3	<0.0001
Prior myocardial infarction*	11%	17%	12%	12%	<0.0001
Extra-cardiac vascular disease					
Aortic disease			35%	32%	<0.0001
Carotid artery disease			12%	29%	<0.0001
Other peripheral vascular disease			59%	49%	<0.0001
Multivessel disease	59%	70%	68%	70%	<0.0001
Target of proximal LAD*	62.0%	62.0%	59.0%	63.0%	0.3
Unprotected LMCA*	8.0%	9.3%	11%	13%	0.0002
Target of CTO*	15%	17%	18%	19%	0.02
Mode of revascularization: CABG*	13%	17%	21%	25%	<0.0001
eGFR <30, not on dialysis*	3.8%	8.5%	6.1%	8.7%	<0.0001
Dialysis*	3.4%	4.8%	9.3%	7.5%	<0.0001
Atrial Fibrillation*	8.9%	16%	10%	17%	<0.0001
Anemia (Hb < 11 g/dl)*	11%	19%	20%	19%	<0.0001
Platelet < $100*10^9$/L*	1.5%	1.5%	3.1%	1.6%	0.01

COPD*	3.4%	4.7%	3.0%	3.2%	0.07
Liver cirrhosis*	2.5%	3.1%	4.1%	2.4%	0.03
Malignancy*	8.9%	9.7%	12%	13%	0.004
(B) Baseline medication					
Medication at hospital discharge					
Antiplatelet therapy					
Thienopyridine	85%	83%	80%	78%	<0.0001
Ticlopidine	90%	91%	92%	90%	0.68
Clopidogrel	9.6%	9.2%	8.4%	10%	
Aspirin	99%	98%	97%	97%	<0.0001
Cilostazole*	18%	18%	16%	14%	0.24
Other medications					
Statins*	50%	41%	40%	36%	<0.0001
Beta-blockers*	30%	28%	24%	23%	<0.0001
ACE-I/ARB*	55%	57%	47%	55%	<0.0001
Nitrates*	35%	38%	35%	32%	0.06
Calcium channel blockers*	40%	48%	53%	56%	<0.0001
Nicolandil*	26%	27%	22%	26%	0.03
Warfarin*	12%	15%	15%	22%	<0.0001
Proton pump inhibitors*	27%	29%	31%	32%	0.04
H2-blockers*	27%	26%	24%	30%	0.03

Values are expressed as mean ± SD.

CAD: coronary artery disease; EVD: extra-cardiac vascular disease; BMI: body mass index; LAD: left anterior descending artery; LMCA: left main coronary artery disease; CTO: chronic total occlusion; CABG: coronary artery bypass grafting, eGFR: estimated glomerular filtration rate; Hb: hemoglobin; COPD: chronic obstructive pulmonary disease; ACE-: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

* Potential independent variables selected for multivariate analysis.

Table 2

Cumulative 3-year incidence of events

	CAD Alone (N=12593) Cumulative Incidence	Stroke and CAD (N=1443) Cumulative Incidence	EVD and CAD (N=974) Cumulative Incidence	Stroke/EVD/CAD (N=253) Cumulative Incidence	P value
MACE	11.2%	19.9%	18.5%	20.1%	<0.0001
All-cause death	9.0%	16.9%	16.1%	16.0%	<0.0001
Cardiovascular death	5.9%	11.4%	10.4%	10.7%	<0.0001
Non-cardiovascular death	3.3%	6.3%	6.3%	6.0%	<0.0001
Myocardial infarction	3.2%	3.5%	4.6%	3.2%	0.34
Stroke	3.9%	9.2%	7.9%	9.6%	<0.0001
Ischemic stroke	3.0%	7.9%	6.0%	6.4%	<0.0001
Hemorrhagic stroke	0.9%	1.4%	2.1%	3.9%	<0.0001
Any coronary revascularization	29.4%	27.0%	30.2%	23.3%	0.02

Cumulative incidence was estimated by the Kaplan-Meier method.

MACE: major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke). Other abbreviations are as in Table1.

Table 3

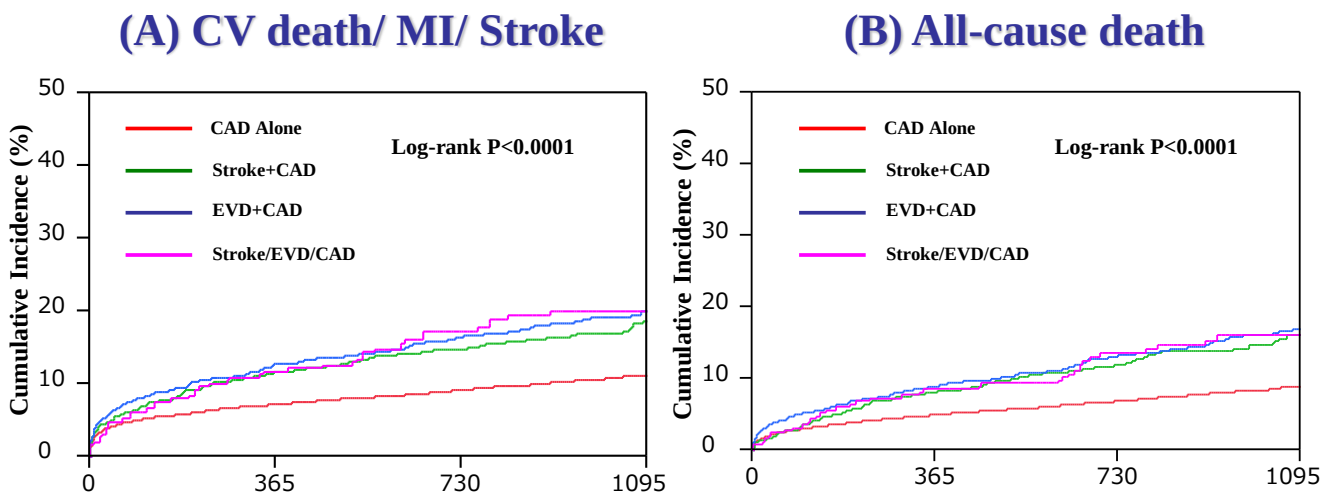
Causes of death during follow-up

	CAD Alone (N=12593)	Stroke and CAD (N=1443)	EVD and CAD (N=974)	Stroke/EVD/CAD (N=253)	P value
Cardiac death	60.8%	56.0%	47.0%	52.8%	0.02
Acute myocardial infarction	21.3%	16.3%	10.5%	11.1%	
Heart failure	10.4%	12.0%	9.0%	16.7%	
Documented VF/ sudden death	7.8%	7.7%	12.7%	8.3%	
Other cardiac death	21.3%	20.1%	14.9%	16.7%	
Vascular death	6.1%	12.9%	17.9%	13.9%	<0.0001
Stroke	4.4%	5.7%	9.7%	5.6%	
Ischemic stroke	1.7%	3.4%	3.0%	0%	
Hemorrhagic stroke	2.6%	2.4%	6.7%	5.6%	
Other vascular death	1.7%	7.2%	8.2%	8.3%	
Non-cardiovascular death	33.1%	31.1%	35.1%	33.3%	0.89
Malignancy	15.4%	9.1%	14.9%	11.1%	
Infection	9.7%	11.0%	9.0%	11.1%	
Other non-cardiovascular death	8.0%	11.0%	11.2%	11.1%	

VF: ventricular fibrillation. Other abbreviations are as in Table1.

Figures

Fig. 1.



Interval	0 day	30 days	1 year	2 years	3 years
CAD Alone					
N of patients with event		478	897	1110	1257
N of patients at risk	12593	11981	11115	8609	4631
Cumulative Incidence		3.8%	7.2%	9.2%	11.2%
Stroke+CAD					
N of patients with event		79	178	224	251
N of patients at risk	1443	1346	1171	855	451
Cumulative Incidence		5.5%	12.7%	16.4%	19.9%
EVD+CAD					
N of patients with event		44	110	138	157
N of patients at risk	974	918	804	605	310
Cumulative Incidence		4.5%	11.6%	14.8%	18.5%
Stroke/EVD/CAD					
N of patients with event		8	29	41	46
N of patients at risk	253	242	210	156	87
Cumulative Incidence		3.2%	11.8%	17.1%	20.1%

Interval	0 day	30 days	1 year	2 years	3 years
CAD Alone					
N of patients with event		252	617	828	987
N of patients at risk	12593	12210	11509	9005	4900
Cumulative Incidence		2.0%	5.0%	6.8%	9.0%
Stroke+CAD					
N of patients with event		51	127	179	209
N of patients at risk	1443	1375	1237	923	493
Cumulative Incidence		3.5%	9.0%	13.2%	16.9%
EVD+CAD					
N of patients with event		16	77	110	134
N of patients at risk	974	946	849	649	336
Cumulative Incidence		1.7%	8.1%	11.9%	16.1%
Stroke/EVD/CAD					
N of patients with event		4	21	32	36
N of patients at risk	253	246	222	167	92
Cumulative Incidence		1.6%	8.5%	13.5%	16.0%

Fig. 2.